

Application No. 10/517,509
Paper Dated: August 2, 2010
In Reply to USPTO Correspondence of March 31, 2010
Attorney Docket No. 0470-045922

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No. : 10/517,509 Confirmation No. : 1291
Applicants : Herman Jan Tijimen Coelingh Bennink et al.
Filed : June 13, 2005
Title : A METHOD OF TREATING HUMAN SKIN AND A
SKIN CARE COMPOSITION FOR USE IN SUCH A
METHOD
Group Art Unit : 1627
Examiner : Samira Jean-Louis
Customer No. : 28289

Mail Stop AF
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF

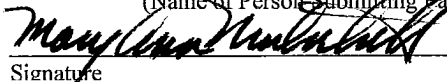
Sir:

For the reasons set forth below, Applicants respectfully submit that the rejections contained within the final Office Action dated March 31, 2010 be withdrawn. The specification provides written support for the phrase "reducing a risk of developing vaginal dryness" even though page 3, lines 8-15, which states "The present method may be applied to human skin which is already dry ... or to healthy skin to prevent or *reduce* such deteriorative changes" (emphasis added). Additionally, the claims are patentable over the cited references because the Applicants have submitted evidence of unexpected results and provided evidence of reasons why one would not have expected estetrol to be pharmacologically useful.

I hereby certify that this correspondence is being electronically submitted to the United States Patent and Trademark Office on August 2, 2010.

Mary Ann Mulvihill

(Name of Person Submitting Paper)


Signature

08/02/2010

Date

Claims 18-19, 24, 26, 28 and 32-34, which are pending in this application, relate to the unexpected finding that estetrol ("E4") is pharmacologically useful in topical treatment of vaginal dryness. These claims stand rejected as not adequately supported by the specification and for obviousness.

**REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH,
WRITTEN DESCRIPTION**

Claims 18-19, 24, 26, 28 and 32-34 have been rejected under 35 U.S.C. § 112, first paragraph, as not being adequately supported by the specification. Applicants' respectfully disagree because page 3, lines 8-15 of the specification states "The present method may be applied to human skin which is already dry ... or to healthy skin to prevent or *reduce* such deteriorative changes" (emphasis added). While "reducing the risk of" encompasses "preventing", the issue under this rejection is whether one would reasonably understand from the specification that the inventors had possession of "reducing the risk of developing vaginal dryness". Since the specification states that the invention reduces deteriorative changes, and since vaginal dryness is caused by deteriorative changes, the specification provides written support for reducing the risk of developing vaginal dryness.

REJECTION UNDER 35 U.S.C. § 103

The pending claims have been rejected under 35 U.S.C. § 103 as obvious in view of the following combination of references:

Claim(s)	Cited References
18, 19, 24, 26, 28, 32-34	Kragie ¹ in view of Willhite ²
18, 19, 24, 26, 28 and 32-34	Sitruk-Ware ³ in view of Spicer ⁴ and Willhite

¹ United States Published Patent Application Number 2004/0192598 to Kragie ("Kragie").

² Willhite *et al.*, "Urogenital Atrophy: Prevention and Treatment," PHARMACOTHERAPY (2001) 21(4): 464-480 ("Willhite").

³ Sitruk-Ware *et al.*, "Local hormonal treatment for urogenital atrophy after menopause," Schweiz. Rundsch., Med. Praxis (1997) 86(33): 1245-1248 ("Sitruk-Ware").

⁴ United States Patent Number 5,211,952 to Spicer ("Spicer").

Before the disclosure of this invention, a person of ordinary skill in the art would not have expected E4 to be pharmacologically useful because it is was known to have a very low estrogen receptor affinity and because it was believed to have a very short *in vivo* elimination half-life like the structural-closely related human estrogens estradiol and estriol. However, the inventors discovered that estetrol has an unexpectedly long half-life. This unexpected long elimination half-life makes E4 surprisingly pharmacologically useful.

The Applicants have filed several patent applications directed to pharmaceutical use of E4. Some of these patent applications have been reviewed by other Examiners in the USPTO, and have been allowed. The other applications directed to uses of E4 and their present statuses are:

U.S. Pat. App. No.	Examiner	Rejections under 35 U.S.C. § 102 or 103
10/478,262	Hui	Rejected under §§ 102 & 103.
10/478,264	Hui	Patented Case (U.S. Pat. No. 7,723,320)
10/478,357	Hui	Pending claims allowed
10/478,365	Chui	Patented Case (U.S. Pat. No. 7,732,430)
10/495,707	Sullivan	Rejected under § 103.
10/517,686	Chui	Prior art rejections have been withdrawn.
10/521,040	Chui	Prior art rejections have been withdrawn.

In these applications, the examiners were persuaded by third-party declarations regarding the unexpected nature of finding that E4 has a long half-life and that it is pharmacologically useful. Similar declarations have been submitted in this application. Yet, the Examiner has not been persuaded by them.

The invention as recited is directed to a method of treating or reducing the risk of vaginal dryness comprising applying a composition containing an estrogenic component to the vaginal epithelium. In one embodiment, the estrogenic component is estetrol.

The Examiner contends “that it would have been well within the purview of the skilled artisan to utilize and to try estetrol since Kragie teaches the use of estetrol as an EFR agent in the treatment of vaginal atrophy and urogenital atrophy and given the teaching of Kragie that weak EFR agent can be used at the appropriate dosage in order to provide sufficient

biological activity for the desired estrogen function at the target site.”⁵ However, one of ordinary skill in the art would not have reasonably expected that estetrol could have been successfully used in a method of treating or reducing a risk of developing vaginal dryness because no one appreciated estetrol’s long half-life, and instead believed that estetrol was not pharmacologically useful due to its low estrogen receptor affinity and its presumed short elimination half-life. In addition, one of ordinary skill in the art would not have reasonably expected that estetrol could successfully be used in the aforementioned method by applying it to the vaginal epithelium (topical administration).

Prior to the publication of this invention, estetrol was known to have a very low affinity for the estrogen receptor. The estrogen receptor affinity of estetrol is about 5% compared to estradiol. Estetrol was also known to have very low estrogen activity. Studies comparing the effect on immature rat uterus of subcutaneously administered estetrol with those of subcutaneously administered estradiol or estrinol showed the estrogenic activity of estetrol to be more than 50 times lower than the estrogenic activity of weak human estrogen estrinol.⁶

Furthermore, estetrol was believed to have a very short half-life because of the chemical similarities to the other human estrogens estradiol and estrinol. Estradiol and estrinol have half-lives of about 30 minutes and 5-10 minutes, respectively. Estrinol has one additional hydroxyl group as compared to estradiol, and estetrol has one additional hydroxyl group than estrinol (or two additional hydroxyl groups as compared to estradiol). It was believed that estetrol, would likewise have a short, if not shorter, half-life.⁷

The inventors have discovered that, contrary to the belief within the art, estetrol actually has a long half-life. Unexpectedly, the Applicants discovered that estetrol has a half-life of about 28 hours.⁸ Due to this unexpected long half-life, estetrol is pharmacologically useful.

⁵ August 18, 2009 Office Action at page 3.

⁶ Declaration by Westhoff at ¶¶ 15-16; Holinka (1979); and Holinka (1980). These studies were done *in vitro*, and therefore, the half-life of estetrol was not measured.

⁷ Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

⁸ Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

Application No. 10/517,509
Paper Dated: August 2, 2010
In Reply to USPTO Correspondence of March 31, 2010
Attorney Docket No. 0470-045922

In addition, Applicant have discovered that estetrol can successfully be used in topical treatment of vaginal dryness.

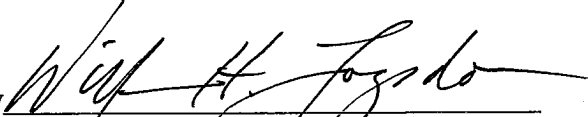
Thus, despite the fact that Kragie mentions estetrol as an example of an EFR agent, one of ordinary skill in the art would not have reasonably expected that he or she could successfully use estetrol in the method taught by Kragie, using topical administration, since, in view on all the pharmacological data about estetrol that was available at the time, it was believed that estetrol was too weak and had too short of a half-life to be useful in topical treatment of vaginal dryness..

CONCLUSION

Accordingly, Applicants respectfully request that the asserted rejections be reconsidered and withdrawn, and that claims 18-19, 24, 26, 28 and 32-34 be allowed.

Respectfully submitted,

THE WEBB LAW FIRM

By 

William H. Logsdon
Registration No. 22,132
Attorney for Applicants
436 Seventh Avenue
700 Koppers Building
Pittsburgh, PA 15219
Telephone: (412) 471-8815
Facsimile: (412) 471-4094
E-mail: webblaw@webblaw.com